REMARKS

This is in response to the Office Action dated July 13, 2004. The specification has been amended as shown above to remove URLs from the specification. No new matter has been added by the amendments to the specification. Claims 1-13 are pending. Claims 9-10 have been cancelled and Claims 1-8 have been amended. Applicants maintain that the amendments add no new matter and are fully supported by the specification as originally filed. For example, support for the amendments to Claims 1-5 can be found in Example 18 beginning at paragraph [0529], as well as paragraph [0336] of the specification.

Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed July 13, 2004. For the reasons set forth below, Applicants respectfully traverse.

Correction of Inventorship under 37 CFR §1.48(b)

Applicant requests that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Specification

URLs:

The Examiner objected to the specification because it contains embedded hyperlinks. Applicants have amended the specification to address the Examiner's concern. In particular, Applicants have replaced the hyperlink with text that describes the location of the website. The amended text no longer constitutes browser executable code.

Continuity:

According to the Office Action, Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 119(e). Specifically, the Examiner asserts that most of the provisional patent applications listed in the first paragraph of the instant specification do not list or refer to SEQ ID NO:88, PRO1270, or Figure 88. Further, the Examiner argues that the instant invention lacks utility. Therefore, the Examiner set as the priority date the filing date of the instant application, May 3, 2002.

Applicants respectfully disagree with the priority date set by the Examiner. In a Preliminary Amendment filed on September 3, 2002, Applicants amended the specification to recite the correct priority for the instant application. The Preliminary Amendment states that the instant "application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/380137 filed 8/25/1999, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/12252 filed 6/2/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/097971 filed 8/26/1998."

The sequences of SEQ ID NOs:87 and 88 were first disclosed in U.S. Provisional Application 60/097971 filed 8/26/1998 in Figures 1 and 2, respectively. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed polypeptides, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. Therefore, the instant application is entitled to an earlier priority date.

Rejection under 35 U.S.C. §101 - Utility

The Examiner rejects Claims 1-13 as allegedly not supported by a specific and substantial asserted utility or a well established utility. The Examiner argues that "the specification does not disclose a function for the polypeptide of SEQ ID NO:88 in the context of the cell or organism." The Examiner asserts that no well established utility exist for newly isolated complex biological molecules.

The Examiner further addresses various utilities set forth in the specification for the claimed polypeptide. One of the discussed possible utilities is use of the claimed polypeptides to detect and treat cancer. The Examiner notes the data in the specification in Example 18 that DNA66308-1537 is over-expressed in normal lung tissue compared to lung tumor tissue. However, the Examiner argues that "evidence of mere expression in a tissue is not tantamount to a showing of a role for the polynucleotide of the present invention." The Examiner continues that "[i]t is not clear if expression of the polynucleotide . . . is correlated with a specific change in physiology, for example, or with a disease state."

The Examiner also argues that protein expression levels cannot be accurately predicted from the level of corresponding mRNA transcript. The Examiner points to one journal article by Haynes *et al.*, as one example showing a lack of correlation between mRNA levels and the expression of protein.

Applicants respectfully disagree and submit that for the reasons stated below, the claimed polypeptides have a credible, substantial, and specific utility.

Utility Guidelines

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." A utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the condition that is to be diagnosed.

The requirement of "substantially utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient*, at least with regard to defining a 'substantial' utility." (M.P.E.P. 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P., 2107 II(B)(1) gives the following instruction to patent examiners: "If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record ... that is probative of the Applicant's assertions." (M.P.E.P. 2107 II(B)(1)(ii)). Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Credible, Specific and Substantial Utility

The Examiner acknowledges that the specification demonstrates that the nucleic acid encoding PRO1270 is expressed at a higher level in normal lung than in lung tumor. However, the Examiner asserts that nucleic acid levels do not correspond to protein levels.

Applicants maintain that the relative nucleic acid levels in normal tissue compared to tumor tissue do correspond to protein levels in normal tissue compared to tumor tissue. Therefore, the difference in expression levels in normal lung cells versus lung tumor cells provides a specific, credible, and substantial utility.

Credible and Substantial Utility

In support of the credible and substantial utility, Applicants submit herewith as Exhibit 1 a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. The first Declaration of J. Christopher Grimaldi describes the techniques used to measure the levels of nucleic acids encoding PRO1270 in normal lung and lung tumors. As stated in Paragraph 6 of the first Declaration of J. Christopher Grimaldi, "Using the widely accepted technique of PCR, it

was determined whether the polynucleotides tested were more highly expressed, less expressed, or whether expression remained the same in tumor tissue as compared to its normal counterpart. Because this technique relies on the visual detection of ethidium bromide staining of PCR products on agarose gels, it is reasonable to assume that any detectable differences seen between two samples will represent at least a two fold difference in cDNA." In Paragraph 7 of the first Declaration, Mr. Grimaldi further states that if a difference in mRNA levels is detected, "this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

Applicants have Established that the Accepted Understanding in the Art is that there is a Direct Correlation between Comparative mRNA Levels and the Level of Expression of the Encoded Protein in Normal versus Cancerous Tissue

The Examiner argues that "[i]t is not clear if expression of the PRO1270 polypeptide is correlated with a specific change in physiology, for example, or with a disease such as cancer." Furthermore, the Examiner argues that "protein expression levels cannot be accurately predicted from the level of corresponding mRNA transcript." The Examiner relies upon Haynes *et al.* (1998, *Electrophoresis*, 19:1862-1871), asserting that Haynes found that for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Even if Haynes supported the Examiner's argument, which it does not, one contrary example does not establish that one of skill in the art would find it is more likely than not, that in general, there is no correlation between mRNA level and protein levels. In fact, the working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels.

Haynes does not contradict the utility of the instant claims. Specifically, Haynes does not address the issue of whether levels of mRNA in a tumor cell compared to a normal cell typically correlate to a similar increase/decrease in the amount of the encoded protein in the tumor cell relative to the normal cell. For example in the case of increased expression of a particular mRNA in a lung tumor cell compared to a non-cancerous lung cell, Haynes does not address whether one would expect to see a corresponding increase in expression of the particular encoded protein in the lung tumor cell compared to the normal lung cell.

Haynes is 1998 a review article dealing with the art of proteome analysis. Haynes studied 80 selected samples, all from one organism, *Saccharomyces cerevisiae*. Haynes considered whether different genes with roughly equivalent mRNA levels would correspond to equivalent protein levels for the different genes. Haynes reported to have "found a general trend but no strong correlation between protein and transcript levels." Thus, it is not even clear that Haynes even supports the Examiner's position, as Haynes did report a general trend, with some exceptions. For some of the studied genes, Haynes reported differences in protein expression between different genes, including some that varied by more than 50-fold. Thus, Haynes showed that for one type of yeast organism, *Saccharomyces cerevisiae*, similar mRNA levels for different genes did not universally result in equivalent protein levels for the different genes. This is different from whether increased mRNA levels for a single gene in one cell type compared to the same gene in a different cell type, would also correspond to increased protein levels in the one cell type compared to the different cell type. Therefore, Haynes is not inconsistent with or contradictory to the utility of the instant claims.

Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 2). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "[t]hose who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 3), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my

> considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, Dr. Polakis and his colleagues have found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceeds this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Additional references support this position. For example, Orntoft et al. (submitted herewith as Exhibit 4) studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method. Orntoft et al. showed that there was a gene dosage effect and teach that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman et al. (submitted herewith as Exhibit 5) showed, using CGH analysis and cDNA microarrays to compare DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there is "evidence of a prominent global influence of copy number changes on gene expression levels" (see page 6244, column 1, last paragraph). Additional supportive teachings are also provided by

Pollack et al. (submitted herewith as Exhibit 6) who studied a series of primary human breast tumors and found that "...62% of highly amplified genes show moderately or highly elevated expression, that DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels" (see column 1, abstract). Thus, these articles collectively teach that in general, there is a correlation between gene expression and mRNA expression.

Taken together, despite some teachings in the art of certain genes that do not fit within this paradigm which are exceptions rather than the rule, in the vast majority of cases, the combined teachings in the art, exemplified by Orntoft et al., Hyman et al. and Pollack et al. and the Grimaldi and Polakis declarations, overwhelmingly teach that gene expression influences mRNA expression and protein levels. Thus, one of skill in the art would reasonably expect, in this instance, based on the gene expression data for the PRO1270 gene, that the PRO1270 protein is concomitantly over-expressed in normal lung cells as compared to lung tumor. Thus, Applicants submit that the PRO1270 protein and the antibodies against this protein have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use these molecules.

The Claimed Polypeptide would have Diagnostic Utility even if there is no Positive Correlation between Gene Expression and Expression of the Encoded Polypeptide

Even assuming *arguendo* that, there is no direct correlation between gene expression and protein expression for PRO1270, which Applicants submit is not true, a polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 2, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 7), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin, submitted herewith (attached as Exhibit 8). The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, a polypeptide encoded by a gene that is differentially expressed in cancer would still have utility. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed polypeptides.

Specific Utility

Applicants assert that the above-discussed substantial utilities are specific to the claimed PRO1270 peptides.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1270 gene in certain types of cancer cells, along with the declarations discussed above, provide a specific utility for the claimed polypeptides.

As discussed above, there are significant data which show that the gene encoding the PRO1270 polypeptide is more highly expressed in normal lung tissue compared to lung tumor tissue. These data are strong evidence that the PRO1270 polypeptide is associated with lung

cancer. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1270 polypeptide with a specific disease. This is a specific utility – it is not a general utility that would apply to polypeptides/proteins generally.

Conclusion

First, the Applicants provide a declaration stating that the data in Example 18 reporting higher expression of the PRO1270 gene in normal lung compared to lung tumor, are real and significant. This declaration also indicates the data provide sufficient comparative and relative expression information and that given the relative difference in expression levels, the claimed polypeptides have utility as cancer diagnostic tools.

Next, Applicants have presented the declarations of two experts in the field along with supporting references which establish that the general, accepted view of those of skill in the art is that there is a direct correlation between mRNA levels and the encoded protein levels. Thus, one of skill in the art would find that it is more likely than not that the claimed polypeptide has utility as a diagnostic tool for cancer.

Applicants have also presented the declarations of two experts in the field, along with supporting references, which establish that even in the anomalous case where there is no positive correlation between gene expression and expression of the encoded protein, the simultaneous monitoring of both is useful for diagnosis and further classification of the cancer.

Finally, Applicants have pointed out that the substantial utilities described above are specific to the claimed polypeptides because PRO1270 is differentially expressed in certain cancer tissue compared to the corresponding normal tissue. This is not a general utility that would apply to the broad class of polypeptides.

As discussed below, Applicants provide herewith several expert opinions supporting the utility of the present invention. Applicants submit that one of ordinary skill in the art would have no legitimate basis to doubt the credibility of the statements made by Mr. Grimaldi, Dr. Polakis and Dr. Ashkenazi and must treat as true the statements made by these experts. Applicants remind the Examiner that "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." PTO Utility Examination Guidelines (2001).

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed polypeptides as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed polypeptides set forth in the specification. Applicants believe that they have met their burden of establishing a specific and substantial credible utility for the claimed invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §101 be withdrawn.

In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. §112, first paragraph – Enablement

The Examiner rejected Claims 1-13 under 35 U.S.C. § 112, first paragraph. According to the Examiner, because the claimed invention is not supported by either a substantial asserted utility or a well established utility, on of skill in the art would not know how to use the invention. The Examiner also argues that the specification does not reasonably provide enablement for all variants of the PRO1270 polypeptide.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. Specifically, the claimed polypeptides have utility in the diagnosis of lung cancer. Also, as set forth above, Claims 1-5 have been amended to recite the functional limitation "wherein said isolated polypeptide is more highly expressed in normal lung tissue compared to lung tumor, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in normal lung tissue compared to lung tumor." Thus, the specification teaches how to make and use the claimed subject matter. Specifically, the specification describes how to make the claimed polypeptides and how to assay for the claimed function in the variant polypeptides. Based upon that teaching and the above-established utility for the claimed subject matter, one skilled in the art would know how to make and use the claimed subject matter.

Therefore, Applicants therefore request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph, based on a lack of utility.

Rejections under 35 U.S.C. §112, first paragraph – Written Description

The Examiner asserts that Claims 1-6, 8-10 and 11-13 contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner notes that the claims are directed to a polypeptide having the sequence of SEQ ID NO:88, variant polypeptides that are 80%-99% identical to SEQ ID NO:88 or various portions or chimeras thereof. However, the Examiner argues that such claims are not described because the specification does not teach functional or structural characteristics of all of the claimed polypeptides.

Applicants have amended the claims to provide that the claimed polypeptides are "more highly expressed in normal lung tissue compared to lung tumor, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in normal lung tissue compared to lung tumor." Accordingly, Applicants maintain that the claims recite sufficient distinguishing characteristics for the claimed genus of polypeptides. Based on the detailed description of the cloning and expression of variants of PRO1270 in the specification, the description of the gene expression assay, the actual reduction to practice of sequences SEQ ID NOs:87 and 88, and the functional recitation in the instant claims, Applicants submit that one of skill in the art would know that Applicants possessed the invention as claimed in the instant claims. Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejections under 35 U.S.C. §112, first paragraph – Deposit Rules

Claims 1-13 are rejected under 35 U.S.C. §112, first paragraph, as not complying with the enablement requirement, for failure to meet the deposit requirement. The Examiner indicates that the requirement can be satisfied by submitting a Declaration by Applicants or assignees or a statement by an attorney of record that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on

this application. Applicants provide the requested Declaration herewith. Although paragraph [446] of the specification states that permanent and unrestricted availability of the deposits will be provided upon issuance of the pertinent U.S. Patent or laying open to the public of any U.S. or foreign patent application, whichever comes first, to facilitate allowance of this application, Applicants provide the requested Declaration herewith.

Rejections under 35 U.S.C. §112, second paragraph

The Examiner has rejected Claims 1-13 under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner objects to the phrase "the extracellular domain" in view of the instant specification implying that the polypeptides are secreted proteins. Claims 9-10 have been cancelled, and the remaining claims have been amended to remove all reference to an extracellular domain. Applicants therefore request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

Conclusion

The present application is believed to be in condition for allowance, and an early action to that effect is respectfully solicited. Applicants invite the Examiner to call the undersigned if any issues may be resolved through a telephonic conversation.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Oct. 12, 2004

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